

# The utility of ETCO<sub>2</sub> value in predicting the progress of the disease and mortality risk in hospitalized patients with COVID-19 pneumonia

## Hastanede yatan COVID-19 hastalarında hastalığın ilerlemesini ve mortalite riskini tahmin etmede ETCO<sub>2</sub> değerlerinin kullanılabilirliği

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### ABSTRACT

**Aim:** End-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) levels are reflective of the ventilatory and metabolic/perfusion status of a patient, regardless of his/her SpO<sub>2</sub> values. This study aimed to investigate the utility of ETCO<sub>2</sub> values in predicting the need for intubation, ICU admission, and mortality in hospitalized patients with COVID-19 pneumonia.

**Material and Method:** A total of 108 hospitalized patients with COVID-19 pneumonia were included. Data on respiratory parameters (oxygen saturation, ETCO<sub>2</sub>, and respiratory rate [RR]- with and without O<sub>2</sub> [w/wo O<sub>2</sub>]) and laboratory parameters were recorded.

**Results:** The need for intensive care unit (ICU) admission was associated with significantly higher ETCO<sub>2</sub> values (wO<sub>2</sub>:27.9 (4.6) vs. 18.6(8.4), p=0.040; woO<sub>2</sub>: 30.1(4.9) vs. 23.8(6.9), p=0.040). Mortality was associated with higher likelihood of higher RR (wO<sub>2</sub>:32.4(5.8) vs. 24.6(6.8), p=0.002) and lower oxygen saturation (wO<sub>2</sub>:92.9(3.8) vs. 95.5(4.2), p=0.025; woO<sub>2</sub>:87.1(5.7) vs. 91.8(6.6), p=0.013). Presence vs. lack of intubation need was associated with significantly increased likelihood of saturation (wO<sub>2</sub>:93.1(5.3) vs. 95.9(3.8), p=0.013; woO<sub>2</sub>:87.6(8.3) vs. 92.3(5.9), p=0.007). Hospital discharge vs. ICU stay was associated with significantly higher ETCO<sub>2</sub> values (wO<sub>2</sub>:27.9 (4.6) vs. 18.6(8.4), p=0.040; woO<sub>2</sub>: 30.1(4.9) vs. 23.8(6.9), p=0.040)

**Conclusion:** Our findings revealed the association of decreased ETCO<sub>2</sub> (w/wo O<sub>2</sub>) values with a lower likelihood of hospital discharge and increased likelihood of ICU transfer. Low oxygen saturation levels related the increased risk of both intubation need and mortality in hospitalized COVID-19 patients.

**Keywords:** COVID-19, intensive care unit, mortality, emergency medicine

### ÖZ

**Amaç:** End-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) seviyeleri, SpO<sub>2</sub> değerlerinden bağımsız olarak hastanın solunum ve metabolik/perfüzyon durumunu yansıtır. Bu çalışma, hastanede yatan COVID-19 hastalarında entübasyon ihtiyacını, yoğun bakım ünitesine kabulünü ve mortaliteyi tahmin etmede ETCO<sub>2</sub> değerlerinin faydasını araştırmayı amaçladı.

**Gereç ve Yöntem:** COVID-19 pnömonisi olan toplam 108 hastanede yatan hasta dahil edildi. Solunum parametreleri (oksijen saturasyonu, ETCO<sub>2</sub> ve solunum hızı [RR]- O<sub>2</sub>'li ve O<sub>2</sub>'siz [w/wo O<sub>2</sub>]) ve laboratuvar parametreleri ile ilgili veriler kaydedildi.

**Bulgular:** COVID-19 hastalarında yoğun bakım ünitesine yatış ihtiyacı, anlamlı olarak daha yüksek ETCO<sub>2</sub> değerleri ile ilişkilendirildi. (wO<sub>2</sub>:27,9 (4,6) vs. 18,6(8,4), p=0.040; woO<sub>2</sub>: 30,1 (4,9) vs. 23,8 (6,9), p=0.040). Mortalite, daha yüksek RR olasılığı (wO<sub>2</sub>:32,4 (5,8) vs. 24,6 (6,8), p=0.002) ve daha düşük saturasyon (wO<sub>2</sub>:92,9 (3,8) vs. 95,5 (4,2), p=0.025; woO<sub>2</sub>: 87,1 (5,7) vs. 91,8(6,6), p=0.013) ile ilişkili bulundu.

**Sonuç:** Bulgularımız, azalmış ETCO<sub>2</sub> (w/wo O<sub>2</sub>) değerlerinin hastaneden taburcu olma olasılığının daha düşük ve yoğun bakım ünitesine transfer olasılığının artmasıyla ilişkisini ortaya koydu. Düşük oksijen saturasyon seviyeleri, hastanede yatan COVID-19 hastalarında hem entübasyon ihtiyacı hem de mortalite riskinin artmasıyla ilişkili bulundu.

**Anahtar Kelimeler:** COVID-19, yoğun bakım ünitesi, mortalite, acil servis

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## INTRODUCTION

Caused by a novel severe coronavirus designated as acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the coronavirus disease-2019 (COVID-19) has become a rapidly spreading pandemic since its onset in Wuhan, China, at the end of 2019 (1,2). COVID-19 has a wide clinical spectrum ranging from asymptomatic or a mild-to-moderate disease with milder symptoms to severe pneumonia with the rapid development of acute respiratory distress syndrome (ARDS) and multiple organ failure and even death (3,4). Notably, early ARDS caused by COVID-19 is considered to significantly differ from the ARDS due to different etiologies in terms of a mismatch between changes in respiratory mechanics and severity of impaired oxygenation, significantly decreased ventilation efficiency and lower lung recruitability (5-7). Hence, the lung tissue in COVID-19 patients recovering from severe ARDS is considered to reflect the typical characteristics of late-phase ARDS (reduced lung compliance, pulmonary fibrosis, and decreased end-expiratory lung volume) but also a more pronounced increase in dead space than in patients with severe ARDS due to other reasons (5,8,9).

The presence of significantly decreased ventilation efficiency and hypermetabolism even in the recovery period in COVID-19 patients is considered to explain the experience of more severe respiratory distress and CO<sub>2</sub> retention by these patients in the late phase of ARDS (9). The ratio of physiologic dead space to tidal volume (VD/VT) at ARDS onset was considered a strong and independent predictor of mortality risk, in addition to its demonstrated utility in detecting lung recruitment and de-recruitment as well as in assessment of the effects of pharmacologic therapies for ARDS (10). Despite its clinical value and wide access to indirect calorimetry and volumetric capnography monitors, measuring VD/VT has not been universally embraced by the larger critical care community, while bedside capnography is much more widely used to measure end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) pressure (PETCO<sub>2</sub>) (10-12). Accordingly, surrogate measures for estimating VD/VT, such as the ratio of ETCO<sub>2</sub> pressure to arterial partial pressure of CO<sub>2</sub> (PETCO<sub>2</sub> /PaCO<sub>2</sub>) and ventilatory ratio have recently been suggested for monitoring pulmonary gas exchange in patients with ARDS (10,13), while its relevance or utility in the COVID-19 related ARDS remains unknown (10,14).

In most cases of COVID-19, adequate-to-low oxygen saturation (SpO<sub>2</sub>) values are maintained initially, and then downturn can occur rapidly, while ETCO<sub>2</sub> levels remain accurate and reflective of the ventilatory and metabolic/perfusion status of a patient, regardless of

his/her SpO<sub>2</sub> values (15-18). In this regard, given the great clinical significance of ascertaining a patient's condition in a timely manner and predicting the progress of the disease (3,4), measurement of ETCO<sub>2</sub> values is considered to play a critical role in detecting the CO<sub>2</sub> level of COVID-19 patients (18,19).

Therefore, this study was designed to investigate the utility of ETCO<sub>2</sub> values in predicting the progress of the disease and mortality risk in hospitalized patients with COVID-19 pneumonia.

## MATERIAL AND METHOD

The study was carried out with the permission of Katip Çelebi University Training and Research Hospital Noninvasive Clinical Researches Ethics Committee (Date: 02.07.2020, Decision No: 2020-GOKAEK-816). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

### Study Population

A total of 108 patients (mean±SD age: years, 50% were males) hospitalized with the diagnoses of COVID-19 pneumonia were included in this prospective cross-sectional study conducted between June 2020 and December 2020 at a tertiary care hospital in Turkey.

### Inclusion Criteria

- Being adult (≥18 years of age)
- Confirmed diagnosis of COVID-19 after laboratory confirmation of SARS-CoV-2 on real-time reverse transcription-polymerase chain reaction (RT-PCR) analysis

### Exclusion Criteria

- Need for Intubation at the time of admission
- Patients with type 1 respiratory failure
- Patients using an oxygen concentrator at home
- Trauma
- Pregnancy
- Pulmonary embolism

### Data Collection

Data on patient demographics (age, gender), presence of comorbid disease, smoking status, systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, body temperature, respiratory parameters including oxygen saturation, ETCO<sub>2</sub> and respiratory rate (RR) – with (4 lt/ and without O<sub>2</sub> (w/wo O<sub>2</sub>), CT findings (Radiological Society of North America chest CT classification system used), need for intubation or intensive care (ICU) stay during hospitalization and laboratory parameters including hemoglobin (Hb, g/dL) and lymphocyte (cells/μL) counts, ferritin (ng/ml), troponin (ng/L), D-Dimer and potassium

(mEq/Lt) levels were recorded in each patient. ETCO<sub>2</sub> measurements were performed on a sidestream capnometry monitor (Vital Sign Monitor VS2000). Immediately after the initial evaluation of the patient was completed, EtCO<sub>2</sub> measurement was performed by the sidestream method by an emergency medicine specialist or an emergency medicine resident. All emergency residents and physicians had in-service training about the standard usage of the sidestream capnography and were informed about the study protocol.

All patients diagnosed with COVID-19 were treated in accordance with the official COVID-19 Adult Treatment Algorithm guidance established by Republic of Turkey Ministry of Health [20]. Patient demographics, comorbid disease, pulmonary involvement, vital signs, respiratory parameters and laboratory parameters were evaluated with respect to ICU admission, intubation need and in hospital mortality.

### Statistical Analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). Pearson Chi-square ( $\chi^2$ ) test, Fisher's exact test and Continuity correction were used for the comparison of categorical data. Mann-Whitney U test and independent sample t-test and ANOVA were used for the parametric variables. Data were expressed as "mean (standard deviation, SD), median (min-max) and percent (%)" where appropriate.  $p < 0.05$  was considered statistically significant.

## RESULTS

Overall, males composed 50% of the study population. Comorbidity was noted in 62.0% of patients and pulmonary involvement was evident in 97.2% (type 1 in 68.5%) of patients. The initial hospitalization unit was general ward in 24 (27.3%) patients and ICU in 84 (72.4%) patients and intubation need was evident in 20 (18.5%) patients (**Table 1**).

ICU admission, the primary outcome of this study, was associated with low ETCO<sub>2</sub> measured both with and without oxygen therapy ( $p=0.006$ ,  $p=0.015$  respectively). Low oxygen saturation, high respiratory rate measured while under oxygen therapy, advanced age, presence of comorbidity and high ferritin were found to be significant in terms of need for intensive care admission ( $p=0.001$ ,  $p=0.001$ ,  $p=0.013$ ,  $p=0.01$  and  $p=0.001$  respectively). The relationship between other factors and the need for ICU hospitalization is presented in **Table 2**.

**Table 1.** Baseline characteristics of the patients (n=108)

|                                     |             |
|-------------------------------------|-------------|
| Gender, n (%)                       |             |
| Female                              | 54 (50)     |
| Male                                | 54 (50)     |
| Comorbidity, n (%)                  |             |
| Present                             | 67 (62)     |
| Absent                              | 41 (38)     |
| CT findings, n (%)                  |             |
| Type 1                              | 74 (68.5)   |
| Type 2                              | 10 (9.3)    |
| Type 3                              | 15 (13.9)   |
| Type 4                              | 9 (8.3)     |
| Pulmonary involvement, n (%)        |             |
| Yes                                 | 105 (97.2)  |
| No                                  | 3 (2.8)     |
| Initial hospitalization unit, n (%) |             |
| ICU                                 | 84 (72.4)   |
| General ward                        | 24 (27.3)   |
| Intubation need, n (%)              |             |
| No                                  | 88 (81.5)   |
| Yes                                 | 20 (18.5)   |
| Mortality                           |             |
| No                                  | 100 (92.6%) |
| Yes                                 | 8 (7.4%)    |

CT: Computed tomography ICU: Intensive care unit

Another primary outcome, the presence of comorbidity, advanced age, low oxygen saturation with and without oxygen therapy, high oxygen-free respiratory rate, low hemoglobin, high ferritin and high D-dimer were found to be significant in terms of increased intubation risk, which is the other primary outcome ( $p=0.01$ ,  $p=0.002$ ,  $p=0.013$ ,  $p=0.007$ ,  $p=0.041$ ,  $p=0.011$ ,  $p=0.012$ ,  $p=0.023$  respectively). The relationship between intubation risk and other parameters is presented in **Table 3**.

Mortality, the secondary outcome of this study, was not associated with ETCO<sub>2</sub> measured both with and without oxygen therapy and comorbid disease presence ( $p=0.190$ ,  $p=0.322$  and  $p=0.15$  respectively). Oxygen saturation with oxygen therapy and respiratory rate were found to be associated with mortality ( $p=0.025$ ,  $p=0.007$  respectively). The relationship between other factors and mortality was presented in **Table 4**.

## DISCUSSION

Our findings in a prospective cohort of patients hospitalized with COVID-19 pneumonia revealed higher likelihood of hospital discharge than ICU stay in patients without comorbidities and those with higher ETCO<sub>2</sub> (w/wo O<sub>2</sub>) values. Presence of comorbidity, older age, high ferritin and D-dimer levels and low hemoglobin levels increased the likelihood of intubation need during hospitalization. High RR with O<sub>2</sub> but low oxygen saturation levels (w/wo O<sub>2</sub>) were the factors associated with increased risk of both intubation need and mortality in hospitalized COVID-19 patients. Intubation need was also associated with increased risk of mortality.

| Table 2. Study parameters with respect to ICU admission need |                        |                       |         |
|--------------------------------------------------------------|------------------------|-----------------------|---------|
|                                                              | Ward (n=88)            | ICU (n=20)            | p value |
| Gender, n (%)                                                |                        |                       |         |
| Female                                                       | 43 (51)                | 11 (46)               | 0.64    |
| Male                                                         | 41 (49)                | 13 (54)               |         |
| Comorbidity, n (%)                                           |                        |                       |         |
| Present                                                      | 45 (54)                | 22 (92)               | 0.01    |
| Absent                                                       | 39 (46)                | 2 (8)                 |         |
| CT findings, n (%)                                           |                        |                       |         |
| Type 1                                                       | 59 (70)                | 15 (62)               | 0.12    |
| Type 2                                                       | 7 (8)                  | 3 (13)                |         |
| Type 3                                                       | 9 (11)                 | 6 (25)                |         |
| Type 4                                                       | 9 (11)                 | 0 (0)                 |         |
| Pulmonary involvement, n (%)                                 |                        |                       |         |
| Yes                                                          | 81 (96)                | 24 (100)              | 1.00    |
| No                                                           | 3 (4)                  | 0 (0)                 |         |
|                                                              | mean(SD;min-max)       | Mean (SD; min-max)    |         |
| Age (year)                                                   | 61.6 (18.9; 19-92)     | 72.3 (12.5; 38-90)    | 0.013   |
| Vital signs                                                  |                        |                       |         |
| Systolic blood pressure (mmHg)                               | 130.1 (18.8; 90-185)   | 132.8 (23.8; 87-183)  | 0.545   |
| Diastolic blood pressure (mmHg)                              | 75.1 (13.5; 11-102)    | 73.5 (10.7; 53-88)    | 0.616   |
| Pulse (bpm)                                                  | 87.1 (18.9; 21-140)    | 86.2 (15.6; 68-132)   | 0.834   |
| Respiratory rate (/min)                                      | 26.8 (5.9; 15-48)      | 28.2 (9.4; 12-48)     | 0.382   |
| Body temperature (°C)                                        | 36.6 (0.6; 35-38)      | 36.4 (0.5; 35-38)     | 0.065   |
| Pulmonary gas exchange                                       |                        |                       |         |
| Saturation – without O <sub>2</sub>                          | 92.4 (5.4; 66.0-100.0) | 88 (9.1; 66.0-98.0)   | 0.001   |
| ETCO <sub>2</sub> without O <sub>2</sub>                     | 30.1 (4.9; 20.0-39.0)  | 27.3 (6.9; 15.0-40.0) | 0.015   |
| RR without O <sub>2</sub>                                    | 27.7 (9.8; 10.0-95.0)  | 28.4 (9.6; 12.0-48.0) | 0.345   |
| ETCO <sub>2</sub> with O <sub>2</sub>                        | 27.9 (4.6; 17.0-39.0)  | 22.9 (7.3; 8.0-38.0)  | 0.006   |
| RR with O <sub>2</sub>                                       | 24.8 (6.7; 10.0-46.0)  | 26.7 (8.0; 9.0-42.0)  | 0.001   |
| Saturation with O <sub>2</sub>                               | 95.9 (3.8; 82.0-100.0) | 93.1 (5.3; 80.0-99.0) | 0.013   |
| Laboratory parameters                                        |                        |                       |         |
| Lymphocyte (10 <sup>3</sup> /μL)                             | 1.8 (1.6; 0.3-9.6)     | 2.8 (5.1; 0.3-22.5)   | 0.746   |
| Hemoglobin (g/dL)                                            | 16.1 (19.5; 6.8-123.0) | 11.4 (2.1; 7.8-14.6)  | 0.271   |
| Ferritin (ng/ml)                                             | 407 (431; 12-1650)     | 770 (683; 66-2457)    | 0.001   |
| Troponin (ng/L)                                              | 0.96 (3.6; 0.0-17.6)   | 0.2 (0.3; 0.0-1.2)    | 0.368   |
| D-Dimer (ng/ml)                                              | 906 (1183; 108-5881)   | 1056 (944; 156-3014)  | 0.439   |
| Potassium (mEq/L)                                            | 4.1 (0.6; 2.4-6.0)     | 4.4 (1.1; 2.8-6)      | 0.484   |

CT: Computed tomography; ETCO<sub>2</sub>: End-tidal CO<sub>2</sub>; RR: respiratory rate; ICU: Intensive care unit, Pearson Chi-Square, Fisher's Exact test, Continuity Correction, Mann-Whitney U test, Independent t test

A remarkably increased physiological dead space is considered likely to be a prominent pathophysiological feature in mechanically ventilated COVID-19 patients recovering from severe ARDS (9). Although the underlying mechanism remains unclear, the proposed mechanisms involve a regional ventilation/perfusion heterogeneity due to loss of lung perfusion regulation and hypoxic vasoconstriction and the pulmonary microthrombosis (5,9,21,22). Our findings indicate that average ETCO<sub>2</sub> in hospitalized COVID-19 patients to be 29.5 mmHg (ranged, 15 to 40 mmHg), while a decrease in ETCO<sub>2</sub> value was associated with increased likelihood of a patient to be transferred to ICU. In addition, both high RR and low saturation (w/wo O<sub>2</sub>) were associated with increased likelihood of intubation need and increased mortality risk among hospitalized COVID-19 patients. Accordingly, our findings support that derangement in gas exchange during ARDS related to COVID-19 is caused by an elevated regional ventilation/perfusion mismatch, which is mainly due to non-perfused but ventilated units (dead space fraction) (23).

Indeed, the presence of increased intrapulmonary shunt in ARDS has been associated with rising PaCO<sub>2</sub> that coincides with decreasing PETCO<sub>2</sub> (24), while alveolar and shunt-associated dead space was reported to account for over half of the measured physiologic dead space as PETCO<sub>2</sub>/PaCO<sub>2</sub> fell to < 0.60 in ARDS not related to COVID-19 (10). Hence, the ratio of PETCO<sub>2</sub>/PaCO<sub>2</sub>, an easily calculated measure with readily available technology at the bedside, has been considered to be beneficial in evaluating pulmonary gas exchange dysfunction in ARDS (10), while PETCO<sub>2</sub>/PaCO<sub>2</sub> < 1 is considered to suggest the presence of elevated intrapulmonary shunt fraction and VD/V also in the COVID-19 setting (14).

Similarly, a decrease in the PETCO<sub>2</sub> /PaCO<sub>2</sub> ratio in early ARDS was reported to be associated with increased VD/VT ratio, oxygenation dysfunction, illness severity scores and increased risk of hospital mortality in ARDS patients (10). Similar to elevated VD/VT in early ARDS, decreasing PETCO<sub>2</sub>/PaCO<sub>2</sub> ratio is also associated with increasing illness severity and mortality risk and thus is

considered likely to be used specifically for monitoring patients with ARDS associated with COVID-19 (10,14). In another study among COVID-19 patients, decreased CO<sub>2</sub> levels, possibly caused by hyperventilation during mechanical ventilation (MV), were reported to increase the mortality risk but had no significant impact on the severity of pneumonia (19). The authors also reported that after adjustment for age, history of cardiovascular disease, WBC, platelet, oxygen support, and lymphocyte count, decreased CO<sub>2</sub> levels remained to be predictor of higher mortality risk in COVID-19 patients (19).

Moreover, the poor prognostic impact of decreased CO<sub>2</sub> levels in COVID-19 patients was also reported to be stronger in case of cardiovascular comorbidity, older age and high D-dimer levels (19). Notably, our findings

revealed that older age, presence of comorbidity and high D-dimer levels were associated with higher risk of intubation need, which was found to be an independent predictor of in-hospital mortality.

In fact, the association of high D-dimer levels with increased the likelihood of intubation need in hospitalized COVID-19 patients in the current study seems also notable given that inflammatory diffuse micro-thrombosis leading to elevated D-dimers, higher pulmonary vascular resistance and larger dead space fraction are considered the key pathophysiological trait of ARDS from COVID-19, while the elevated D-dimers are also considered an independent predictor of mortality and enlarged pulmonary vessels in COVID-19 patients with ARDS (23,25,26).

**Table 3.** Study parameters with respect to intubation need

|                                          | Intubation need            |                            | p value |
|------------------------------------------|----------------------------|----------------------------|---------|
|                                          | No (n=88)                  | Yes (n=20)                 |         |
| Gender, n (%)                            |                            |                            |         |
| Female                                   | 44 (50.0)                  | 10 (50.0)                  | 1.00    |
| Male                                     | 44 (50.0)                  | 10 (50.0)                  |         |
| Comorbidity, n (%)                       |                            |                            |         |
| Present                                  | 49 (55.7)                  | 18 (90.0)                  | 0.01    |
| Absent                                   | 39 (44.3)                  | 2 (10.0)                   |         |
| CT findings, n(%)                        |                            |                            |         |
| Type 1                                   | 63 (71.6)                  | 11 (55.0)                  | 0.26    |
| Type 2                                   | 7 (8.0)                    | 3 (15.0)                   |         |
| Type 3                                   | 10 (11.4)                  | 5 (25.0)                   |         |
| Type 4                                   | 8 (9.1)                    | 1 (5.0)                    |         |
| Pulmonary involvement, n(%)              |                            |                            |         |
| Yes                                      | 86 (97.7)                  | 19 (95.0)                  | 0.38    |
| No                                       | 2 (2.3)                    | 1 (5.0)                    |         |
|                                          | Mean (SD;min-max)          | Mean (SD;min-max)          |         |
| Age (year)                               | 61.5 (18.6;19.0-92.0)      | 75.1 (10.2;52.0-90.0)      | 0.002   |
| Vital signs                              |                            |                            |         |
| Systolic blood pressure (mmHg)           | 130.7 (18.6;90.0-185.0)    | 130.7 (24.7;87.0-183.0)    | 0.997   |
| Diastolic blood pressure (mmHg)          | 75.5 (13.5;11.0-102.0)     | 71.2 (9.4;53.0-88.0)       | 0.182   |
| Pulse (bpm)                              | 87.2 (18.7;21.0-140.0)     | 85.5 (15.9;68.0-132.0)     | 0.334   |
| Respiratory rate (/min)                  | 26.8 (6.4;15.0-48.0)       | 28.8 (8.4;12.0-48.0)       | 0.241   |
| Body temperature (°C)                    | 36.6 (0.6;35.8-38.8)       | 36.4 (0.5;35.9-38.0)       | 0.147   |
| Pulmonary gas exchange                   |                            |                            |         |
| Saturation – without O <sub>2</sub>      | 92.3 (5.9;66.0-100.0)      | 87.6 (8.3;66.0-98.0)       | 0.007   |
| ETCO <sub>2</sub> without O <sub>2</sub> | 29.7 (5.3;20.0-39.0)       | 28.6 (6.3;15.0-40.0)       | 0.429   |
| RR without O <sub>2</sub>                | 27.6 (10.0;10.0-95.0)      | 29.0 (8.6;12.0-48.0)       | 0.041   |
| ETCO <sub>2</sub> with O <sub>2</sub>    | 27.3 (5.4;7.6-39.2)        | 24.5 (6.3;14.0-38.0)       | 0.570   |
| RR with O <sub>2</sub>                   | 24.9 (6.8;10.0-46.0)       | 26.6 (8.0;9.0-42.0)        | 0.329   |
| Saturation with O <sub>2</sub>           | 95.9 (3.8;80.0-100.0)      | 93.1 (5.3;81.0-99.0)       | 0.013   |
| Laboratory parameters                    |                            |                            |         |
| Lymphocyte (10 <sup>3</sup> /μL)         | 3.8 (19.4;0.3-183.0)       | 2.7 (5.0;0.3-22.5)         | 0.277   |
| Hemoglobin (g/dL)                        | 15.0 (16.3;6.8-123.0)      | 11.0 (2.3;7.8-14.6)        | 0.011   |
| Ferritin (ng/ml)                         | 417.8 (481.7;9.0-2457.0)   | 700.4 (546.4;115.0-1650.0) | 0.012   |
| Troponin (ng/L)                          | 0.8 (3.3;0.0-17.6)         | 0.2 (0.3;0.0-1.2)          | 0.157   |
| D-Dimer (ng/ml)                          | 856.0 (1093.1;85.0-5881.0) | 1245.1 (1006.5;156-3014)   | 0.023   |
| Potassium (mEq/L)                        | 4.1 (0.6;2.4-6.0)          | 4.2 (0.9;2.9-5.8)          | 0.893   |

CT: Computed tomography; ETCO<sub>2</sub>: End-tidal CO<sub>2</sub>; RR: respiratory rate; ICU: Intensive care unit, Pearson Chi-Square, Fisher's Exact test, Continuity Correction, Mann-Whitney U test, Independent t test

**Table 4.** Study parameters with respect to survival

|                                                                                                                                                                                                                                  | Survival status  |                       |                    |                           | p value |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|-----------------------|--------------------|---------------------------|---------|
|                                                                                                                                                                                                                                  | Survivor (n=100) |                       | Non-survivor (n=8) |                           |         |
| Gender, n (%)                                                                                                                                                                                                                    |                  |                       |                    |                           | 0.72    |
| Female                                                                                                                                                                                                                           |                  | 51 (51)               |                    | 3 (38)                    |         |
| Male                                                                                                                                                                                                                             |                  | 49 (49)               |                    | 5 (63)                    |         |
| Comorbidity, n (%)                                                                                                                                                                                                               |                  |                       |                    |                           | 0.15    |
| Present                                                                                                                                                                                                                          |                  | 60 (60)               |                    | 7 (87)                    |         |
| Absent                                                                                                                                                                                                                           |                  | 40 (40)               |                    | 1 (12)                    |         |
| CT findings, n (%)                                                                                                                                                                                                               |                  |                       |                    |                           | 0.40    |
| Type 1                                                                                                                                                                                                                           |                  | 70 (70)               |                    | 4 (50)                    |         |
| Type 2                                                                                                                                                                                                                           |                  | 8 (8)                 |                    | 2 (25)                    |         |
| Type 3                                                                                                                                                                                                                           |                  | 14 (14)               |                    | 1 (12)                    |         |
| Type 4                                                                                                                                                                                                                           |                  | 8 (8)                 |                    | 1 (12)                    |         |
| Pulmonary involvement, n (%)                                                                                                                                                                                                     |                  |                       |                    |                           | 0.53    |
| Yes                                                                                                                                                                                                                              |                  | 98 (98)               |                    | 7 (88)                    |         |
| No                                                                                                                                                                                                                               |                  | 2 (2)                 |                    | 1 (12)                    |         |
|                                                                                                                                                                                                                                  | n                | Mean (SD; min-max)    | n                  | Mean (SD; min-max)        | p value |
| Age (year)                                                                                                                                                                                                                       | 100              | 63.5 (18.6;19-92)     | 8                  | 70.5 (7.6; 58-78)         | 0.435   |
| Vital signs                                                                                                                                                                                                                      |                  |                       |                    |                           |         |
| Systolic blood pressure (mmHg)                                                                                                                                                                                                   | 100              | 130.8 (19.6; 90-185)  | 8                  | 128.8 (23.7; 87-155)      | 0.777   |
| Diastolic blood pressure (mmHg)                                                                                                                                                                                                  | 100              | 74.9 (13.0; 11-102)   | 8                  | 71.6 (11.5; 53-88)        | 0.489   |
| Pulse (bpm)                                                                                                                                                                                                                      | 100              | 86.2 (18.0; 21-140)   | 8                  | 95.1 (18.7; 77-132)       | 0.231   |
| Respiratory rate (/min)                                                                                                                                                                                                          | 100              | 26.6 (6.6; 12-48)     | 8                  | 33.4 (6.9; 26-48)         | 0.007   |
| Body temperature (°C)                                                                                                                                                                                                            | 100              | 36.6 (0.6; 35.8-38.8) | 8                  | 36.5 (0.3; 36-36)         | 0.795   |
| Pulmonary gas exchange                                                                                                                                                                                                           |                  |                       |                    |                           |         |
| Saturation – without O <sub>2</sub>                                                                                                                                                                                              | 100              | 91.8 (6.6; 66-100)    | 8                  | 87.1 (5.7; 79-95)         | 0.013   |
| ETCO <sub>2</sub> without O <sub>2</sub>                                                                                                                                                                                         | 100              | 29.7 (5.4; 20-40)     | 8                  | 27.7 (6.5; 15-35)         | 0.322   |
| RR without O <sub>2</sub>                                                                                                                                                                                                        | 100              | 27.4 (9.8; 10-95)     | 8                  | 34.3 (6.5; 26-48)         | 0.053   |
| ETCO <sub>2</sub> with O <sub>2</sub>                                                                                                                                                                                            | 100              | 27.0 (5.7; 7.6-39.2)  | 8                  | 24.3 (5.8; 14-32)         | 0.190   |
| RR with O <sub>2</sub>                                                                                                                                                                                                           | 100              | 24.6 (6.8; 9-46)      | 8                  | 32.4 (5.8; 26-42)         | 0.002   |
| Saturation with O <sub>2</sub>                                                                                                                                                                                                   | 100              | 95.5 (4.2; 80-100)    | 8                  | 92.9 (3.8; 87-98)         | 0.025   |
| Laboratory parameters                                                                                                                                                                                                            |                  |                       |                    |                           |         |
| Lymphocyte (10 <sup>3</sup> /μL)                                                                                                                                                                                                 | 100              | 3.5 (18.2; 0.3-183)   | 8                  | 4.7 (7.6; 0.6-22.5)       | 0.819   |
| Hemoglobin (g/dL)                                                                                                                                                                                                                | 100              | 14.4 (15.4; 6.8-123)  | 8                  | 12.2 (2.1; 9.1-14.4)      | 0.925   |
| Ferritin (ng/ml)                                                                                                                                                                                                                 | 87               | 471 (516; 9-2457)     | 7                  | 442 (317; 115-967)        | 0.522   |
| Troponin (ng/L)                                                                                                                                                                                                                  | 82               | 0.8 (3.1; 0-17.6)     | 7                  | 0.(0; 0-0)                | 0.375   |
| D-Dimer (ng/ml)                                                                                                                                                                                                                  | 92               | 909 (1087; 85-5881)   | 7                  | 1163.1 (1083.7; 218-3014) | 0.319   |
| Potassium (mEq/L)                                                                                                                                                                                                                | 99               | 4.2 (0.6; 2.4-6)      | 7                  | 4.2 (1.1; 2.9-5.8)        | 0.745   |
| CT: Computed tomography; ETCO <sub>2</sub> : End-tidal CO <sub>2</sub> ; RR: respiratory rate; ICU: Intensive care unit, Pearson Chi-Square, Fisher’s Exact test, Continuity Correction, Mann-Whitney U test, Independent t test |                  |                       |                    |                           |         |

CT: Computed tomography; ETCO<sub>2</sub>: End-tidal CO<sub>2</sub>; RR: respiratory rate; ICU: Intensive care unit, Pearson Chi-Square, Fisher's Exact test, Continuity Correction, Mann-Whitney U test, Independent t test

Our findings are consistent with previous data on the association of decreased ETCO<sub>2</sub> levels with poor prognosis in COVID-19 patients, supporting the likelihood of elevated ventilation-perfusion mismatch due to high dead space fraction to be a specific characteristic of this syndrome that may provide important insights for clinical treatment recommendations (9,19,23). Notably, potential for lung recruitment in patients with ARDS from COVID-19 is considered highly variable and use of simple bedside estimates of recruitability is recommended to guide personalized MV settings (23). Although, shortness of breath, reduction of pulmonary perfusion and increased alveolar dead space and MV hyperventilation have been considered amongst the reasons for decreased CO<sub>2</sub> levels (17,19,27), since most COVID-19 patients

require various forms of oxygen support, among other treatment, clinicians are recommended to focus on MV hyperventilation to prevent a decrease in the CO<sub>2</sub> levels due to hyperventilation as an effective and practical measure to improve patients' survival and to adjust oxygen flow in accordance with patients' requirements to treat pneumonia (19,28).

Certain limitations to this study should be considered. First, potential lack of generalizability is an important limitation due to single-center study design with relatively small sample size. Second, lack of data on other surrogate measures for estimating VD/VT, such as PETCO<sub>2</sub> /PaCO<sub>2</sub> ratio or ventilatory ratio seems to be another limitation of the present study.

## CONCLUSION

Our findings in a prospective cohort of hospitalized patients with COVID-19 pneumonia revealed the association of decreased ET<sub>CO<sub>2</sub></sub> (w/wo O<sub>2</sub>) values with lower likelihood of hospital discharge and increased likelihood of ICU transfer. Although ET<sub>CO<sub>2</sub></sub> values per se had no significant impact on survival status, presence of comorbidity, older age, high D-dimer levels increased the likelihood of intubation need during hospitalization, while initial general ward hospitalization, high RR (wO<sub>2</sub>) but low oxygen saturation levels (w/woO<sub>2</sub>) predicted the increased risk of both intubation need and mortality in hospitalized COVID-19 patients. In this regard, our findings emphasize the clinical significance of ET<sub>CO<sub>2</sub></sub>-based dynamic monitoring of pulmonary gas exchange as combined with patient age, comorbidity status and peripheral blood parameters in patients with COVID-19 related ARDS, in assisting clinicians to identify patients at an increased risk of worse outcomes and thus to provide timely tailored treatment in those with potentially dismal prognosis.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of Katip Çelebi University Training and Research Hospital Noninvasive Clinical Researches Ethics Committee (Date: 02.07.2020, Decision No: 2020-GOKAEK-816).

**Informed Consent:** All patients signed the free and informed consent form.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

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**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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